IDENTIFYING TARGET POPULATIONS & DESIGNING CLINICAL TRIALS FOR ANTIEPILEPTOGENESIS

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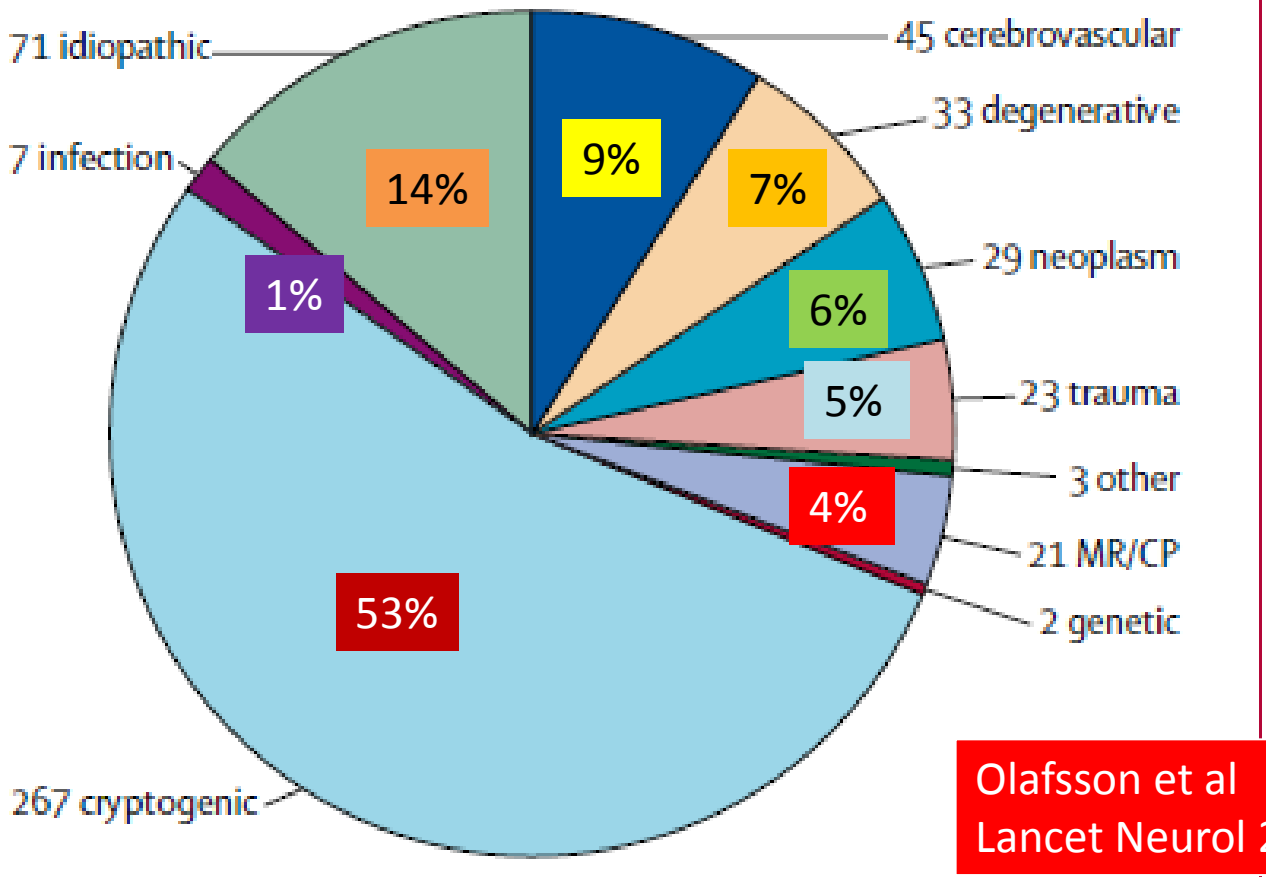
OUTLINE

- Definitions & background risks in epilepsy
- End-points
- Target populations & sample size
- Blindness & placebo
- Duration of treatment & follow-up
- Methodological & practical issues
- Conclusions

EPILEPSY AND EPILEPTIC SEIZURES

- **EPILEPSY** = Condition characterized by recurrent unprovoked seizures
- **UNPROVOKED SEIZURE** = Seizure occurring in the absence of known precipitants; it may occur even at the presence of a stable CNS disorder
- **ACUTE SYMPTOMATIC (PROVOKED) SEIZURE** = Seizure occurring in close temporal relation with an acute systemic, metabolic, or toxic CNS injury

CAUSES OF UNPROVOKED SEIZURES

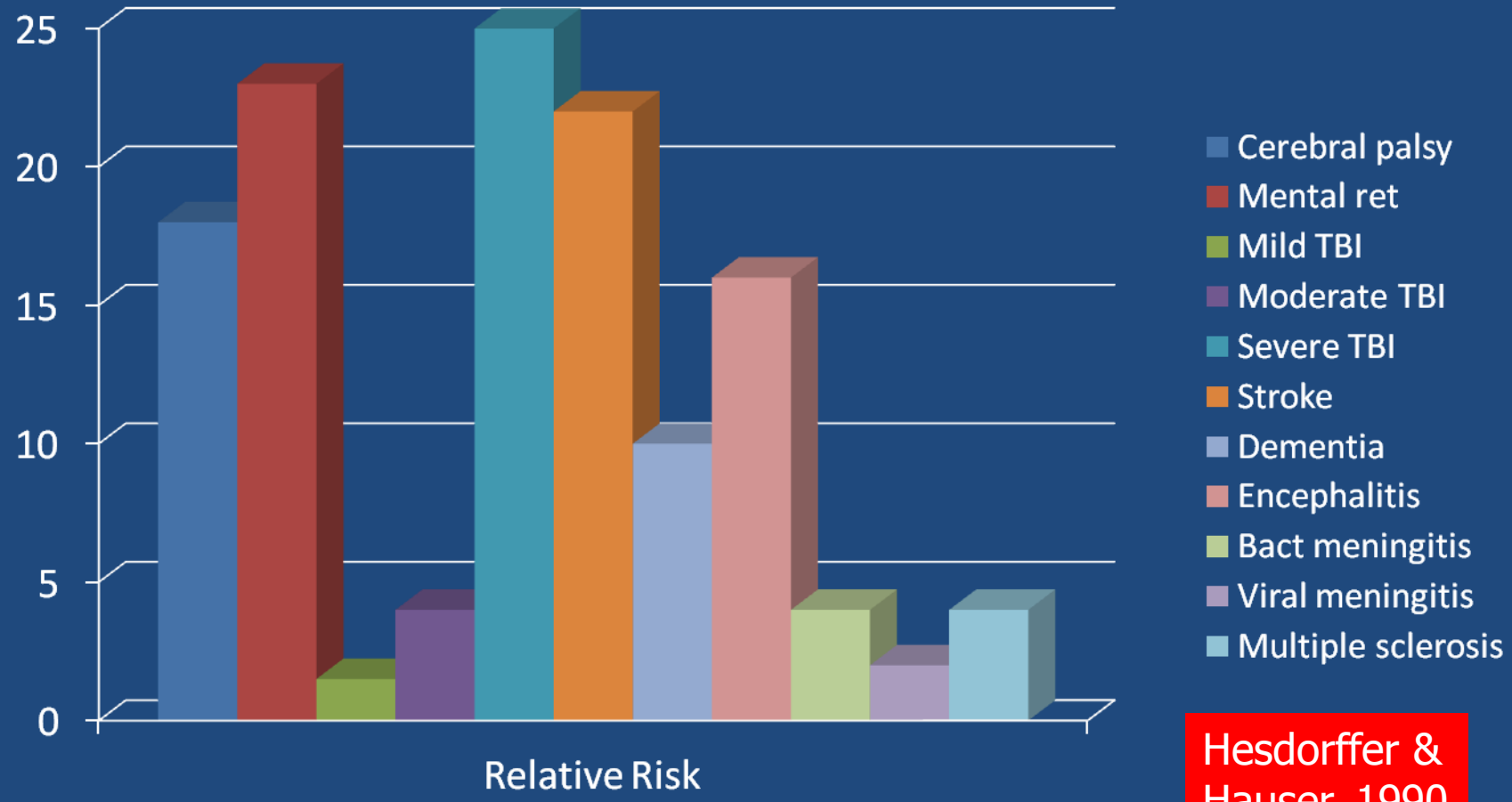


N = 501

Olafsson et al
Lancet Neurol 2005

Preventable etiologies = 25%

RISK OF EPILEPSY IN DIFFERENT CLINICAL CONDITIONS



Hesdorffer & Hauser, 1990

RISK OF SEIZURES & EPILEPSY AFTER TBI, STROKE & BRAIN INFECTION

Clinical condition	TBI	Stroke	Encephalitis	Bacterial meningitis
Incidence (N per 100,000/year)	180-250	100-200	7	9
Acute symptomatic seizures (%)	2-17	≤ 6	44	18
Unprovoked seizures/epilepsy at 1 year (%)	6 (severe)	5	2 (includes aseptic meningitis)	
Unprovoked seizures/epilepsy at 5 years (%)	10 (severe)	11	3 (includes aseptic meningitis)	
Unprovoked seizures/epilepsy at 10 years (%)	13 (severe)	-	10	3

Annegers JF et al. Neurology 1988; 38:1407-1410; Annegers JF et al. New Eng J Med 1998; 338:20-24; Beghi E et al. Ann Neurol 1984; 16: 283-294; Beghi E et al. Neurology 2011; 757: 1785-1793, Bruns J, Hauser WA. Epilepsia 2003; 44 (suppl 10): 2-10; Burn J et al. BMJ 1997; 315:1582-1587; Feigin V et al. Lancet Neurol 2008; 9: 355-369 ; Frey LC Epilepsia 2003; 44 (suppl 10): 11-17; Nicolosi A et al. J Infect Dis 1986; 154:399-408.

RISK FACTORS FOR SEIZURES & EPILEPSY AFTER TBI, STROKE & BRAIN INFECTION

Clinical condition	Risk Factors
TBI	Penetrating wound, intracerebral hemorrhage, depressed skull fracture, acute symptomatic seizures
STROKE	Cerebral hemorrhage, cortical lesion (ischemic), size (ischemic), acute symptomatic seizures (ischemic)
Encephalitis	Acute symptomatic seizures
Bacterial meningitis	Acute symptomatic seizures

Annegers JF et al. Neurology 1988; 38:1407-1410; Annegers JF et al. New Eng J Med 1998; 338:20-24; Burn J et al. BMJ 1997; 315:1582-1587.

PREVENTION OF SEIZURES AFTER TBI
Target Populations & Sample Size

Type of traumatic brain injury (TBI)	% with unprovoked seizures at 1 yr	No. patients to enroll in clinical trial
All patients	0.6	2368
Patients with severe head trauma	5.8	262
Patients with brain contusion	6.3	242
Patients with subdural hematoma	5.5	278
Patients with depressed skull fracture	4.2	366
Patients with acute symptomatic seizures	5.1	300

Source: Annegers JF et al. New Eng J Med 1998; 338:20-24

ISSUES WITH END-POINTS IN ANTIEPILEPTOGENESIS STUDIES

- Absence of seizures (any)
- Absence of unprovoked seizures
- Absence of repeated unprovoked seizures (epilepsy)
- 50% risk reduction (50% reduction of cases expected to develop seizures)

DURATION OF TREATMENT & FOLLOW-UP

- Treatment for the entire study duration or for a limited time period
- Duration of follow-up depends on the probability of occurrence of the measured events (disease varieties & comorbidities)
- Drop-outs to be considered (sample size)

BLINDNESS & PLACEBO

- Double-blind, single-blind or open trial
  - Ethical issues
  - Practical issues
  - Regulatory issues
  - Methodological issues
- Placebo vs. no treatment
  - Same as above

METHODOLOGICAL & PRACTICAL ISSUES

- Frequency of end-points (ie, seizure occurrence) depends on the risk factor
- Characteristics of study (sub)populations are key
- Robustness & generalizability of the results
- Drop-out rate must be anticipated
- Duration of follow-up is instrumental for the success of the trial
- Patients with TBI, stroke & infection must be assessed separately

CONCLUSIONS

- Antiepileptogenesis trials can be performed in well-defined at-risk populations
- Within each clinical condition, patients at high risk of seizures are the best target population
- Patients should be stratified into homogeneous subgroups – **need of biomarkers**
- There are pros & cons with blinding & placebo
- Duration of treatment and follow-up can be optimised to prevent drop-outs and collect a sizable number of events